UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/785,532	01/17/1997	JOE W. GRAY	2500.124US2	4124

22798 7590 03/11/2003

QUINE INTELLECTUAL PROPERTY LAW GROUP, P.C.
P O BOX 458
ALAMEDA, CA 94501

EXAMINER	
DAVIS, MINH TAM B	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 03/11/2003

35

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	08/785,532	GRAY ET AL.	
	Examiner	Art Unit	
	MINH-TAM DAVIS	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 November 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *26-63* is/are pending in the application.

4a) Of the above claim(s) *29-36,38-55 and 57-60* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *26-28,37,56 and 61-63* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *See Continuation Sheet* .

Continuation of Attachment(s) 6). Other: courtesy copies of prior search reports in 1997.

DETAILED ACTION

Effective February 7, 1998, the Group Art Unit location has been changed, and the examiner of the application has been changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Minh-Tam Davis, Group Art Unit 1642.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant s submission filed on 11/25/02 has been entered.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Accordingly, claims 26-28, 37, 56, 61-63, SEQ ID NO:9 are examined in the instant application.

REJECTION UNDER 35 USC 112, SECOND PARAGRAPH

Claims 26-28, 37, 56, 61-63 remain rejected under 35 USC 112, second paragraph pertaining to the use of the language "relative" copy number in claim 26, for reasons already of record in paper No: 28.

Applicant argues that the term "relative copy number" is a term well known in the art, as shown in the paragraph on CGH microarrays obtained from a web site. Applicant

asserts that the term indicates simply that the measurement, while quantitative need not be an absolute measure of copy number.

The recitation of the paragraph on CGH microarrays is acknowledged.

Applicant's arguments in paper No: 33 have been considered but are found not persuasive for the following reasons:

It is noted that in the paragraph on CGH microarrays, the relative copy number in the test sample is recited as comprared to the control sample (3rd page, first paragraph). In claim 26 however, it is not clear that the relative copy number of a nucleic acid in a sample is relative to what and/or is compared to what.

Further, there is no definition of the term "relative copy number" in the specification, nor in the CGH microarrays paragraph recited by Applicant.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, WRITTEN DESCRIPTION

Claims 26-28, 56, 61-63 remain rejected under 35 USC 112, first paragraph pertaining to lack of a clear written description, for reasons already of record in paper No: 28.

Applicant argues that Applicant were in possession of a probe which hybridizes to SEQ ID NO:9 under the stringent conditions recited in claim 26. Applicant asserts that the Examiner has offered no objective evidence that such numerous unrelated sequences would be detected in the assay.

Applicant's arguments in paper No: 33 have been considered but are found not persuasive for the following reasons:

The claims as written encompass a method for detecting the presence or absence of neoplastic cells having an increased copy number of nucleic acid sequences at chromosome region 20q13.2, using probes with unknown structure and length, provided said probes share a fragment with SEQ ID NO:9 and are capable of hybridizing to SEQ ID NO:9 via said common fragment under the stringent conditions recited in claim 26.

The specification and the claims lack information of the structure or function of the probes used for the claimed method, and thus do not meet the written description requirement.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, ENABLEMENT, NEW REJECTION

Claims 26-28, 37, 56, 61-63 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 26-28, 37, 56, 61-63 are drawn to a method of detecting in a sample the presence or absence of neoplastic cells having an increased copy number of nucleic acid sequences at chromosome region 20q13.2, comprising contacting a nucleic acid sample with a probe which hybridizes to SEQ ID NO:9, under the stringent conditions recited in claim 26, and detecting the formation of a hybridization complex to determine the relative copy number of a nucleic acid in the chromosome region 20q13.2, thereby

identifying the presence or absence of neoplastic cells having an increased copy number of nucleic acid sequences at the chromosomal region 20q13.2.

The specification discloses that using the minimal chromosomal region probe RMC20C001 which is within the chromosome region 20q13.2, an increased level of DNA amplication in the region encompassed by said probe is consistently detected in breast cancers (p.49-50). The specification also discloses that the RMC20C001 probe defines a region of 1.5 Mb within the chromosome region 20q13.2 (p.52, last paragraph). The specification further discloses that SEQ ID NO:9 represent the 2Kb promoter region of zinc finger amplified in breast cancer (ZABC-1), and that this gene maps to the core of the 20q13.2 amplicon and is overexpressed in primary tumors and breast cancer cell lines (p.21, lines 11-15).

No data however is found in the specification concerning the detection of an increased copy number of the gene comprising SEQ ID NO:9. Further, it is not clear whether overexpression of the gene comprising SEQ ID NO:9 is referred to gene amplification or RNA amplification, which are independent from each other .

One cannot extrapolate the teaching of the specification to the scope of the claims because although the 1.5 Mb RMC20C001 probe detect DNA amplication in this region, the RMC20C001 probe spans a very large region of 1.5 Mb which comprises numerous genes that are unrelated to the gene comprising SEQ ID NO:9, which comprises of only a 2Kb sequence, and because it is well known in the art that amplification or regulation of different genes is independent of each other. In other words, it is unpredictable which genes in the 1.5 Mb region are amplified and detected

by the RMC20C001 probe. Thus one cannot predict that detection of the presence of SEQ ID NO:9 in a sample would detect an increased copy number of the gene comprising SEQ ID NO:9, and it is not clear how the detection of the presence of SEQ ID NO:9 would determine the relative copy number of a nucleic acid in the chromosome region 20q13.2, and thereby indentifying the presence of neoplastic cells.

Further, no specific probes are recited in the claims for use in the detection of SEQ ID NO:8. One would have expected that using any probe, non-related nucleic acid sequences, which share some similarity with SEQ ID NO:9, could be detected, thus could effect the total level of DNA detected. For example, the claimed method would detect 1) a sequence which is 88% similar to SEQ ID NO:9, as taught by Morris et al, 1991 (MPSRCH search report, 1997, us-08-731-499-05.rge, pages 1-2, of record, a courtesy copy of which is enclosed) 2) a sequence which is 84% similar to SEQ ID NO:9, as taught by Ionov Y et al, 1994 (MPSRCH search report, 1997, us-08-731-499-01.rng, page 2, of record, a courtesy copy of which is enclosed) and 3) a sequence which is 77% similar to SEQ ID NO:9, as taught by Beach DH et al, 1993 (MPSRCH search report, 1997, us-08-731-499-01.rng, pages 1-2, of record, a courtesy copy of which is enclosed), wherein these unrelated sequences are not necessarily amplified. In other words, using any probe, it is unpredictable that one could detect an increase in the gene copy of SEQ ID NO:9 in cancer as compared to normal control, due to possible interference by other unrelated sequences that are also detected.

In view of the above, it would have been undue experimentation for one of skill in the art to practice the claimed invention as broadly as claimed.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, SCOPE

1. If Applicant could overcome the above 112, first paragraph rejection, claims 26-28, 56, 61-63 are still rejected under 35 USC 112, first paragraph, pertaining to lack of enablement for a method for detecting the presence or absence of "any neoplastic cell" having an increased number of "any nucleic acid sequence" at chromosome region 20q13.2, for reasons already of record in paper No: 28.

Applicant argues that that the Examiner implicitely reads a limitation into the claims that is not present. Applicant asserts that the language "any neoplastic cells" or "any nucleic acid sequences" does not exist in claim 26, and invites the Examiner to identify the language "any neoplastic cells" or "any nucleic acid sequences" in claim 26.

Applicant asserts that genes other than those identified in the present claims may also be amplified at 20q13.2 in neoplastic cells is simply irrelevant to enablment of the claimed invention.

Applicant asserts that the Examiner has provided no objective basis to support an allegation that performing the presently claimed method will fail to identify amplifications at 20q13.2 in a sample containing cells having such amplification.

Applicant's arguments in paper No: 33 have been considered but are found not persuasive for the following reasons:

It is noted that the language "any neoplastic cells" or "any nucleic acid sequences" does not have to be in the claim 26 for the claim 26 to be reasonably interpreted as encompassing a method for detecting the presence or absence of "any

neoplastic cell" having an increased number of "any nucleic acid sequence" at chromosomal region 20q13.2, by detecting the hybridization of a probe with SEQ ID NO:9, wherein detecting the formation of a hybridization complex would determine the relative copy number of "any nucleic acid" in chromosomal region 20q13.2, thereby indentifying the presence or absence of any neoplastic cells having an increased copy number of "any nucleic acid sequence" at chromosomal region 20q13.2.

One cannot extrapolate from one example of detection of breast cancer, in which SEQ ID NO:9 is overexpressed, to detection of any cancer having increased copy of number of a nucleic acid sequence which is unrelated to SEQ ID NO:9, provided said nucleic acid sequence is within the chromosome region 20q13.2, because using a probe specific for SEQ ID NO:9 one would not expect to detect other sequences that are structurally unrelated to SEQ ID NO:9, but are within the chromosome region 20q13.2. Further, although breast cancer has overexpression of SEQ ID NO:9, it is unpredictable that any other neoplastic cell that has an increased copy number of nucleic acid sequences at chromosome region 20q13.2, wherein said nucleic acid sequences are different than SEQ ID NO:9, would also have an increased copy number of SEQ ID NO:9, because different cancers have different etiology, and mechanisms of carcinogenesis, and because the role of SEQ ID NO:9 in any cancer development is not known.

2. If Applicant could overcome the above 112, first paragraph rejection, claims 26-28, 56, 61-63 are still rejected under 35 USC 112, first paragraph pertaining to lack of enablement for a method for detecting in "any sample", the presence or absence of

neoplastic cells having an increased number of nucleic acid sequences at chromosome region 20q13.2, for reasons already of record in paper No: 28.

Applicant argues that in a sample lacking neoplastic cells with an amplification at 20q13.2, the assay will be negative, i.e. the assay will report the absence of neoplastic cells in the subject sample as recited in the preamble of the claim.

Applicant's arguments in paper No: 33 have been considered but are found not persuasive for the following reasons:

The claims encompass a method for detecting the presence of neoplastic cells in any sample. However, it is unpredictable that any cancer sample, or any cancer tissue would have an increased copy of SEQ ID NO:9, because different cancers have different etiology, and mechanisms of carcinogenesis, and because the role of SEQ ID NO:9 in any cancer development is not known.

Further, there is no use for the claimed detection of the absence of neoplastic cells in a sample, e.g. in a hair sample.

In view of the above, it would have been undue experimentation to practice the claimed invention as broadly as claimed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINH-TAM DAVIS whose telephone number is 703-305-2008. The examiner can normally be reached on 9:30AM-4:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, ANTHONY CAPUTA can be reached on 703-308-3995. The fax phone

numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0916.

MINH TAM DAVIS

February 4, 2003

ANTHONY C. CAPUTA
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

MPSRCH (TM)

Release 2.1D John F. Collins, Biocomputing Research Unit.


```
MPsrch_nn   n.a. - n.a. database search, using Smith-Waterman algorithm

Run on:       Sun Jun 29 03:22:08 1997; MasPar time 1852.43 Seconds
                                        1200.504 Million cell updates/sec
Tabular output not generated.

Title:        >US-08-731-499-9
Description:  (7201-9200) from US08731499.seq (5 of 6)
Perfect Score: 2000
N.A. Sequence: 7201 TATTACCTCAATATTCATCT..........AAGCAGAGCCCTCCTGGGCC 9200
     Comp:          ATAATGGAGTTATAAGTAGA..........TTCGTCTCGGGAGGACCCGG

Scoring table: TABLE default
               Gap 6

Nmatch: STD :  Dbase 0; Query 0

Searched:      333249 seqs, 555961234 bases x 2

Post-processing: Minimum Match 0%
                 Listing first 45 summaries

Database:      embl-new11
                1:BCT 2:FUN 3:GEN 4:HUM1 5:HUM2 6:HUM3 7:INV1 8:INV2
                9:INV3 10:INV4 11:INV5 12:INV6 13:INV7 14:ORG 15:MAM
                16:VRT 17:PLN 18:PRO1 19:PRO2 20:ROD 21:SYN 22:UNC
                23:VIR1 24:VIR2
Database:      genbank97
                25:BCT1 26:BCT2 27:BCT3 28:BCT4 29:BCT5 30:BCT6 31:BCT7
                32:BCT8 33:BCT9 34:GEN1 35:GEN2 36:HTG 37:INV1 38:INV2
                39:INV3 40:INV4 41:INV5 42:INV6 43:INV7 44:INV8 45:INV9
                46:MAM1 47:MAM2 48:MAM3 49:VRT1 50:VRT2 51:VRT3 52:PAT1
                53:PAT2 54:PAT3 55:PAT4 56:PHG 57:PLN1 58:PLN2 59:PLN3
                60:PLN4 61:PLN5 62:PLN6 63:PLN7 64:PLN8 65:PLN9 66:PLN10
                67:PRI1 68:PRI2 69:PRI3 70:PRI4 71:PRI5 72:PRI6 73:PRI7
                74:PRI8 75:PRI9 76:PRI10 77:PRI11 78:PRI12 79:PRI13
                80:PRI14 81:ROD1 82:ROD2 83:ROD3 84:ROD4 85:ROD5 86:ROD6
                87:ROD7 88:ROD8 89:STR 90:SYN 91:UNA 92:VRL1 93:VRL2
                94:VRL3 95:VRL4 96:VRL5 97:VRL6 98:VRL7 99:VRL8 100:VRL9
Database:      genbank-new11
                101:BCT 102:GEN 103:INV1 104:INV2 105:MAM 106:VRT
                107:PHG 108:PLN 109:PRI1 110:PRI2 111:ROD 112:SYN
                113:UNA 114:VRL
Database:      u-embl48_97
                115:part1 116:part2

Statistics:    Mean 12.230; Variance 6.274; scale 1.949
```

Pred. No. is the number of results predicted by chance to have a score greater than or equal to the score of the result being printed, and is derived by analysis of the total score distribution.

SUMMARIES

	Result No.	Score	Query Match	Length	DB	ID	Description	Pred. No.
	1	204	10.2	152141	73	HSU07000	Human breakpoint clus	2.15e-130
c	2	202	10.1	2928	70	HSAPOA2G	Human gene for apolip	8.49e-129
c	3	202	10.1	3360	70	HSAPOA2	Human gene for apolip	8.49e-129
c	4	203	10.1	158827	110	HSK217C2	Human DNA sequence fr	1.35e-129
	5	200	10.0	7407	76	HUMGIPRD	Human gene for gastri	3.34e-127
c	6	200	10.0	26764	76	HUMDODDA	Homo sapiens deoxycyt	3.34e-127
	7	200	10.0	37194	75	HSV210E9	Human DNA sequence fr	3.34e-127
	8	200	10.0	84539	70	HSABLGR3	Human proto-oncogene	3.34e-127
c	9	200	10.0	116879	74	HSU47924	Human chromosome 12p1	3.34e-127
c	10	200	10.0	222930	109	HSU47924	Human chromosome 12p1	3.34e-127
	11	197	9.9	4208	69	HS91K3D	Human DNA sequence fr	8.20e-125
	12	197	9.9	36594	79	HUMTPA	Human tissue plasmino	8.20e-125
	13	197	9.9	38538	70	HSE95B1	Human DNA sequence fr	8.20e-125
c	14	198	9.9	40227	72	HSN119A7	Human DNA sequence fr	1.31e-125
c	15	198	9.9	40227	110	HSN119A7	Human DNA sequence fr	1.31e-125
c	16	198	9.9	40509	75	HSU73E8	Human DNA sequence fr	1.31e-125
	17	197	9.9	49625	6	HSB13C9	Human DNA sequence fr	8.20e-125
	18	197	9.9	49625	4	HSB13C9	Human DNA sequence fr	8.20e-125
	19	197	9.9	49625	110	HSB13C9	Human DNA sequence fr	8.20e-125
	20	197	9.9	49625	5	HSB13C9	Human DNA sequence fr	8.20e-125
	21	198	9.9	90000	36	HSAC000010	EPM1/APECED region of	1.31e-125
	22	198	9.9	90000	4	HSAC10	EPM1/APECED region of	1.31e-125
	23	198	9.9	90000	6	HSAC10	EPM1/APECED region of	1.31e-125
	24	198	9.9	90000	5	HSAC10	EPM1/APECED region of	1.31e-125
	25	199	9.9	115062	110	HSK799F10	Human DNA sequence fr	2.09e-126
c	26	197	9.9	120000	5	HSAC00003	Chromosome 17 genomic	8.20e-125
c	27	197	9.9	120000	36	HSAC000003	Chromosome 17 genomic	8.20e-125
c	28	197	9.9	120000	4	HSAC00003	Chromosome 17 genomic	8.20e-125
c	29	197	9.9	120000	6	HSAC00003	Chromosome 17 genomic	8.20e-125
	30	198	9.9	140787	110	HSJ293L6	Human DNA sequence fr	1.31e-125
	31	199	9.9	144401	110	HSJ104C13	Human DNA sequence fr	2.09e-126
	32	199	9.9	155821	110	HSJ78B3	Human DNA sequence fr	2.09e-126
	33	199	9.9	164393	110	HSJ272J12	Human DNA sequence fr	2.09e-126
c	34	196	9.8	16397	71	HSL60G9B	Human DNA sequence fr	5.13e-124
	35	196	9.8	30110	71	HSL124H12	Human DNA sequence fr	5.13e-124
c	36	196	9.8	37194	75	HSV210E9	Human DNA sequence fr	5.13e-124
	37	195	9.8	40176	109	HSU58675	Human olfactory recep	3.20e-123
	38	196	9.8	40905	110	HSN87F1	Human DNA sequence fr	5.13e-124
c	39	195	9.8	44888	67	HS130N4B	Human DNA sequence fr	3.20e-123
	40	195	9.8	68468	78	HUMMMDBC	Human DNA from cosmid	3.20e-123
	41	196	9.8	95819	110	HSK286B10	Human DNA sequence fr	5.13e-124
	42	195	9.8	106000	74	HSU40455	Human chromosome X co	3.20e-123
	43	195	9.8	111344	4	HS17	Human DNA sequence fr	3.20e-123
	44	195	9.8	111344	6	HS17	Human DNA sequence fr	3.20e-123
c	45	196	9.8	163037	110	HSJ6802	Human DNA sequence fr	5.13e-124

ALIGNMENTS

```
RESULT      1
LOCUS       HSU07000   152141 bp    DNA             PRI       17-JAN-1996
DEFINITION  Human breakpoint cluster region (BCR) gene, complete cds.
ACCESSION   U07000
NID         g487344
KEYWORDS    .
SOURCE      human.
  ORGANISM  Homo sapiens
            Eukaryotae; mitochondrial eukaryotes; Metazoa; Chordata;
            Vertebrata; Eutheria; Primates; Catarrhini; Hominidae; Homo.
REFERENCE   1  (bases 1 to 152141)
  AUTHORS   Chissoe,S.L., Bodenteich,A., Wang,Y.F., Wang,Y.P., Burian,D.,
            Clifton,S.W., Crabtree,J., Freeman,A., Iyer,K., Jian,L., Ma,Y.,
            McLaury,H.-J., Pan,H.-Q., Sarhan,O.H., Toth,S., Wang,Z., Zhang,G.,
            Heisterkamp,N., Groffen,J. and Roe,B.A.
  TITLE     Sequence and analysis of the human ABL gene, the BCR gene, and
            regions involved in the Philadelphia chromosomal translocation
  JOURNAL   Genomics 27 (1), 67-82 (1995)
  MEDLINE   95394474
REFERENCE   2  (bases 14590 to 16317; 87877 to 88058; 95028 to 95132; 95433 to
            95618; 102486 to 102593; 105610 to 105670; 107159 to 107211; 107712
            to 107852; 118055 to 118176; 119111 to 119279; 121237 to 121356;
            122175 to 122250; 123595 to 123699; 124417 to 124491; 126619 to
```

library
JOURNAL Science 216 (4550), 1136-1138 (1982)
MEDLINE 82199444
REFERENCE 24 (sites)
AUTHORS Soekarman,D., van Denderen,J., Hoefsloot,L., Moret,M., Meeuwsen,T., van Baal,J., Hagemeijer,A. and Grosveld,G.
TITLE A novel variant of the bcr-abl fusion product in Philadelphia chromosome-positive acute lymphoblastic leukemia
JOURNAL Leukemia 4 (6), 397-403 (1990)
MEDLINE 90294679
REFERENCE 25 (sites)
AUTHORS Heisterkamp,N., Stephenson,J.R., Groffen,J., Hansen,P.F., de Klein,A., Bartram,C.R. and Grosveld,G.
TITLE Localization of the c-abl oncogene adjacent to a translocation break point in chronic myelocytic leukaemia
JOURNAL Nature 306 (5940), 239-242 (1983)
MEDLINE 84068136
REFERENCE 26 (sites)
AUTHORS Grosveld,G., Verwoerd,T., van Agthoven,T., de Klein,A., Ramachandran,K.L., Heisterkamp,N., Stam,K. and Groffen,J.
TITLE The chronic myelocytic cell line K562 contains a breakpoint in bcr and produces a chimeric bcr/c-abl transcript
JOURNAL Mol. Cell. Biol. 6 (2), 607-616 (1986)
MEDLINE 87064346
REFERENCE 27 (sites)
AUTHORS Morris,C.M., Heisterkamp,N., Groffen,J. and Fitzgerald,P.H.
TITLE Entire ABL gene is joined with 5'-BCR in some patients with Philadelphia-positive leukemia
JOURNAL Blood 78 (4), 1078-1084 (1991)
MEDLINE 91329820
REFERENCE 28 (sites)
AUTHORS Heisterkamp,N., Knoppel,E. and Groffen,J.

8/13/97

Note: remainder of annotations omitted.

Query Match 10.2%; Score 204; DB 73; Length 152141;
Best Local Similarity 88.7%; Pred. No. 2.15e-130;
Matches 251; Conservative 0; Mismatches 29; Indels 3; Gaps 3;

```
Db  86498 ttcttttctttttctttttttttt-tttttgagacagagtcttgctctgtcacctaggct 86556
          ||| |||||||||||| |||||| |||||||||| |||||||||||||||||| ||||
Qy   7427 TTCATTTCTTTTCTTTCTTTTTTGTTTTTTGAGACGGAGTCTTGCTCTGTCACCTCGGCT 7486

Db  86557 ggagtgcagtggtgcaatctggctcactgcaacctccacctcccaggttcaagcgattc 86616
          |||||||||||||||||| |||||||||| |||||||||| ||||||||| || |
Qy   7487 GGAGTGCAGTGGTGCAATTTCGGCTCACTGCAGCCTCCACCTCCCTGGTTCAAGCAATAC 7546

Db  86617 tcctgcctcagcctcctgagtagctgggattacaggcacctgccaccatgcccacctaat 86676
          |||||||||||||||| |||||||||||| |||||||||| ||| |||||
Qy   7547 TCCTGCCTCAGCCTCCCCAGTAGTTGGGATTACAGGTACCTGCCACCACACCCGGCTAAT 7606

Db  86677 tttttatagttttagtagagatggggtt-caccatattggccaggctggtctcgaactcc 86735
          || | ||||||||||||||||||||| |||||| |||||||||||| |||||||||
Qy   7607 TTCTG-TATTTTTAGTAGAGATGGGGTTTCACCATGCTGGCCAGGCTGGTTTCGAACTCC 7665

Db  86736 tgacctcaagtgatccacccacctcggcctcccaaagtgctgg 86778
          |||||||||||||||| |||||||||| |||| |||
Qy   7666 TGACCTCAAGTGATCCGCTCACCTTGGCCTCCCATAGTGTTGG 7708
```

RESULT 2

LOCUS HSAPOA2G 2928 bp DNA PRI 14-MAR-1995
DEFINITION Human gene for apolipoprotein AII.
ACCESSION X02905
NID g28757
KEYWORDS Alu repetitive sequence; apolipoprotein A-II; inverted repeat; terminal repeat; Z DNA.
SOURCE human.
ORGANISM Homo sapiens
Eukaryotae; mitochondrial eukaryotes; Metazoa; Chordata; Vertebrata; Eutheria; Primates; Catarrhini; Hominidae; Homo.
REFERENCE 1 (bases 1 to 2928)
AUTHORS Knott,T.J., Wallis,S.C., Robertson,M.E., Priestley,L.M., Urdea,M., Rall,L.B. and Scott,J.
TITLE The human apolipoprotein AII gene: structural organization and sites of expression
JOURNAL Nucleic Acids Res. 13 (17), 6387-6398 (1985)
MEDLINE 86016095
REFERENCE 2 (bases 715 to 2456)
AUTHORS Lackner,K.J., Law,S.W. and Brewer,H.B. Jr.
TITLE The human apolipoprotein A-II gene: complete nucleic acid sequence and genomic organization
JOURNAL Nucleic Acids Res. 13 (12), 4597-4608 (1985)
MEDLINE 85242123
COMMENT Data kindly reviewed (18-DEC-1985) by J. Scott.

FEATURES	Location/Qualifiers
source	1..2928
	/organism="Homo sapiens"
repeat_region	556..565
	/note="direct repeat 1"
repeat_region	573..582
	/note="direct repeat 2"
repeat_region	591..600
	/note="direct repeat 2"
repeat_region	607..616
	/note="direct repeat 1"
repeat_region	703..712
	/note="direct repeat 3"
repeat_region	730..739
	/note="direct repeat 3"
CAAT_signal	834..842
	/note="put. CAAT-like sequence"
TATA_signal	883..888
exon	912..945
	/number=1
mRNA	join(912..945,1115..1190,1484..1616,2012..2241)
prim_transcript	912..2241
misc_RNA	912
	/note="major cap site"
misc_RNA	916
	/note="minor cap site"
conflict	replace(943..944,"taggtaagataagga")
	/note="ta is taggtaagataagga in [2]"
	/citation=[2]
intron	946..1114
	/note="intron I"
conflict	replace(989,"t")
	/note="c is t in [2]"
	/citation=[2]
conflict	replace(1019,"t")
	/note="c is t in [2]"
	/citation=[2]
exon	1115..1190
	/number=2
sig_peptide	join(1139..1190,1484..1485)
CDS	join(1139..1190,1484..1616,2012..2129)
	/codon_start=1
	/product="apo AII"
	/db_xref="PID:g296634"
	/db_xref="SWISS-PROT:P02652"
	/translation="MKLLAATVLLLTICSLEGALVRRQAKEPCVESLVSQYFQTVTDY GKDLMEKVKSPELQAEAKSYFEKSKEQLTPLIKKAGTELVNFLSYFVELGTQPATQ"
intron	1191..1483
	/note="intron II"
conflict	replace(1415,"g")
	/note="a is g in [2]"
	/citation=[2]
misc_feature	1446..1477
	/note="(GT)x16, pot. zDNA structure"
exon	1484..1616
	/number=3
mat_peptide	join(1501..1616,2012..2126)
	/product="mature apo AII"
conflict	replace(1530,"g")
	/note="a is g in [2]"
	/citation=[2]

Release 2.1D John F. Collins, Biocomputing Research Unit.

MPsrch_nn n.a. - n.a. database search, using Smith-Waterman algorithm

Run on: Sat Jun 28 22:40:56 1997; MasPar time 213.20 Seconds
867.829 Million cell updates/sec

Tabular output not generated.

Title: >US-08-731-499-9
Description: (1-2000) from US08731499.seq (1 of 6)
Perfect Score: 2000
N.A. Sequence: 1 CCATCATATTTCTTATTTTT.....AAAATAGTTTACTAAAGTGT 2000
Comp: GGTAGTATAAAGAATAAAAA.....TTTTATCAAATGATTTCACA

Scoring table: TABLE default
Gap 6

Nmatch STD : Dbase 0; Query 0

Searched: 121476 seqs, 46255616 bases x 2

Post-processing: Minimum Match 0%
Listing first 45 summaries

Database: n-geneseq26
1:part1 2:part2 3:part3 4:part4 5:part5 6:part6 7:part7
8:part8 9:part9 10:part10 11:part11 12:part12 13:part13
14:part14 15:part15 16:part16 17:part17 18:part18
19:part19 20:part20 21:part21 22:part22 23:part23

Statistics: Mean 9.913; Variance 8.353; scale 1.187

Pred. No. is the number of results predicted by chance to have a score greater than or equal to the score of the result being printed, and is derived by analysis of the total score distribution.

SUMMARIES

	Result No.	Score	% Query Match	Length	DB	ID	Description	Pred. No.
c	1	135	6.8	3158	9	Q53212	Human cyclin D3 promo	1.64e-48
c	2	135	6.8	3158	5	Q31880	Cyclin D3 promoter.	1.64e-48
c	3	121	6.1	283	11	Q63862	AP2 sequence obtd. by	8.37e-42
	4	120	6.0	7849	16	Q94109	hML genomic DNA.	2.51e-41
c	5	118	5.9	1618	7	Q46958	Human cytokine synthe	2.25e-40
c	6	118	5.9	1618	2	Q10207	pH15C insert containi	2.25e-40
	7	118	5.9	6511	14	Q95493	Human Cdn-2 DNA.	2.25e-40
	8	117	5.8	321	8	Q59208	Human brain Expressed	6.73e-40
	9	117	5.8	321	6	Q39796	Expressed Sequence Ta	6.73e-40
c	10	116	5.8	335	8	Q60863	Human brain Expressed	2.01e-39
c	11	117	5.8	2600	1	N90029	Human interleukin-1 r	6.73e-40
c	12	117	5.8	2600	12	Q73764	Human IL-1 receptor g	6.73e-40
c	13	117	5.8	2600	1	N90118	cDNA of human interle	6.73e-40
c	14	117	5.8	2963	8	Q49933	IL-1R cDNA.	6.73e-40
	15	117	5.8	3234	15	Q92781	Human thymopoietin ge	6.73e-40
c	16	115	5.8	11531	9	Q54222	BSSL/CEL Gene.	6.01e-39
c	17	117	5.8	17327	7	Q44278	Serglycin - proteogly	6.73e-40
	18	114	5.7	4823	22	T37384	Human thrombopoietin	1.79e-38
	19	114	5.7	4823	17	T03943	Human thrombopoietin	1.79e-38
	20	114	5.7	4823	16	T04051	Sequence encoding hae	1.79e-38
c	21	112	5.6	2435	23	T33155	Tissue plasminogen ac	1.59e-37
c	22	112	5.6	2888	1	Q03743	Human SKI related gen	1.59e-37
	23	112	5.6	6905	15	Q92779	Human thymopoietin co	1.59e-37
c	24	111	5.6	8363	15	Q92408	Human cyclin A gene.	4.75e-37
	25	112	5.6	17327	7	Q44278	Serglycin - proteogly	1.59e-37
	26	112	5.6	22481	23	T11658	PEDF full length sequ	1.59e-37
c	27	110	5.5	2649	6	Q35034	DNA fragment contg. A	1.41e-36
	28	110	5.5	7620	6	Q39286	Glucocerebrosidase ge	1.41e-36
c	29	110	5.5	10684	23	T33758	Control region isolat	1.41e-36
c	30	109	5.4	308	8	Q60826	Human brain Expressed	4.20e-36
c	31	109	5.4	743	2	N70812	Sequence encoding hum	4.20e-36
	32	109	5.4	2660	3	N30032	Sequence of gene for	4.20e-36
	33	108	5.4	4382	2	Q12759	P40 genomic DNA.	1.25e-35
c	34	108	5.4	6063	6	Q37205	Delta-amino levulinat	1.25e-35
	35	108	5.4	10897	19	T09187	MuTu putative oncogen	1.25e-35
c	36	109	5.4	13585	17	T11549	Tumour rejection anti	4.20e-36
c	37	109	5.4	30967	23	T32454	Calpain large subunit	4.20e-36
c	38	106	5.3	366	8	Q60353	Human brain Expressed	1.10e-34
c	39	107	5.3	1777	12	Q79355	Sequence of the exten	3.70e-35
	40	107	5.3	2320	4	Q26657	glut4 promoter/enhanc	3.70e-35
c	41	107	5.3	2339	2	Q10956	Encodes human 75kD TN	3.70e-35
c	42	107	5.3	2425	18	T11027	DNA encoding the huma	3.70e-35
c	43	107	5.3	2425	20	T10283	Gene for RNA componen	3.70e-35
c	44	106	5.3	5359	17	T12251	Cytochrome P450 isoen	1.10e-34
c	45	107	5.3	9272	12	Q79353	Human genomic clone h	3.70e-35

ALIGNMENTS

RESULT 1
ID Q53212 standard; DNA; 3158 BP.
AC Q53212;
DT 22-JUN-1994 (first entry)
DE Human cyclin D3 promoter.
KW D-type; mammalian; CLN protein; protein deficiency; cell cycle start;
KW yeast; complement; ds.
OS Homo sapiens.
FH Key Location/Qualifiers
FT misc_feature 3156..3158
FT /*tag= a
FT /note= "initiation ATG codon"
PN WO9324514-A.
PD 09-DEC-1993.
PF 25-MAY-1993; U05000.
PR 26-MAY-1992; US-888178.
PA (MITO-) MITOTIX.
PI Beach DH.
DR WPI; 93-405720/50.
PT New D-type mammalian cyclin - replaces CLN-type protein needed
PT for cell start in budding yeast and is detected by antibodies or
PT hybridisation in biological samples to determine abnormal cell
PT division
PS Disclosure; Fig 13; 108pp; English.
CC The sequence is that of human cyclin D3 promoter.
SQ Sequence 3158 BP; 952 A; 674 C; 722 G; 810 T;

8/13/97

Query Match 6.8%; Score 135; DB 9; Length 3158;
Best Local Similarity 77.0%; Pred. No. 1.64e-48;
Matches 221; Conservative 0; Mismatches 62; Indels 4; Gaps 2;

```
Db   1653 ggccgggaacggtggctcacgcctgtaatcccagcacttttggaggccgagaccggcgga 1712
           || |||| | |||||||||| ||| || |||||   |||| ||| |||||    || |||
Cp    293 GGACGGGTATAGTGGCTCACACCTATACTCCCAATGCTTTGGGAAGCCGAAGTGGGTGGA 234

Db   1713 tcac--gaggtcaggggttcaagactagcctggccaacatagtgaaaccccatctctacg 1770
           ||||  |||| |||| |||  |||| ||||||||||||||| |||||||||| | ||| |
Cp    233 TCACATGAGGCCAGGAGTTGGAGACCAGCCTGGCCAACATGGTGAAACCCCTTATCTGCT 174

Db   1771 aaaaatacaaaaattagtcaggcatggtggtgcgtgcctgtagtcccagctactcgggaa 1830
           ||||||||||||||||||   ||||||||  | |   |||||| |||||||||| | |||||
```

```
Qy   173 AAAAATACAAAAATTAGCTGGGCATGGTAATACACACCTGTAATCCCAGCTATTTGGGAA 114

Db  1831 ttgcttgaacccgggaggtggaggttgcagtgagcccagatcgcaccactgcactccagc 1890
         |  |||||||| |||||||||||||||||||||| ||||||||||||||   ||||||
Cp   113 TCACTTGAACCCAGGAGGTGGAGGTTGCAGTGAGCCAAGATCGCACCACTGG--TCCAGC 56

Db  1891 ttgagcaacagagtagacttcgtctcaaaaaaaaaaaaaaaaaaaaa 1937
           || |||||||| |     ||  |||       ||||||| || |||
Cp    55 CTGGGCAACAGAGCAAGTCTCCCCTCTCCGCCCAAAAAAATAAGAAA 9


RESULT    2
ID   Q31880 standard; DNA; 3158 BP.
AC   Q31880;
DT   22-APR-1993  (first entry)
DE   Cyclin D3 promoter.
KW   Cyclin; D1; D2; D3; promoter; human; liver; genomic library; clone;
KW   upstream; exon; intron; neural; pCYCD1-H12; mutant; yeast; strain;
KW   CLN; cyclin; gene; CLN 1; CLN 2; human; glioblastoma; cDNA library;
KW   expression vector; pADNS; transformant; pCYCD1-21; pCYCD1-19; HeLa;
KW   ss.
OS   Homo sapiens.
PN   WO9220796-A.
PD   26-NOV-1992.
PF   18-MAY-1992; U04146.
PR   16-MAY-1991; US-701514.
PA   (COLD-) COLD SPRING HARBOR LAB.
PI   Beach DH;
DR   WPI; 92-415774/50.
PT   Recombinant mammalian D-type cyclin - replaces a CLN-type protein
PT   essential for cell start in budding yeast, its antibodies and
PT   probes being useful in detecting D-type cyclin in biological
PT   samples
PS   Disclosure; Fig 13; 75pp; English.
CC   The sequences given in Q31878-80 represents the cyclin D1 to D3
CC   promoters.  These sequences were identified during the isolation of
CC   the D-type cyclin cDNAs from a normal human liver genomic library.
CC   A mutant yeast strain in which two of the three CLN cyclin genes
CC   (CLN 1 and CLN 2) were inactivate and expression of the third was
CC   conditional, was used to identify human cDNA clones that rescue yeast
CC   from CLN deficiency.  A human glioblastoma cDNA library carried in a
CC   yeast expression vector (pADNS) was introduced into a mutant yeast
CC   strain.  Two yeast transformants (pCYCD1-21 and pCYCD1-19) which grew
CC   despite the lack of function of all three CLN genes and were not
CC   revertants, were identified and recovered in E. coli.  These two
CC   clones were shown to be independent clone representing the same gene.
CC   A HeLa cDNA library was screen for a full length cDNA clone using the
CC   1.2 kb insert of pCYCD1-21 as a probe.  The sequence isolated by this
CC   method was pCYCD1-H12 (see also Q31873).  Degenerate probes and
CC   primers were designed using the D1 gene sequence.  These primers
CC   and probes were used in the isolation of the cyclin D2 and D3 genes.
CC   See also Q31874-5.  The cyclin D1 cDNA clone was used to screen a
CC   liver genomic library resulting in the identification of three
CC   positive clones.  These clones were shown to correspond to the
CC   upstream promoter region and a 198 bp exon, followed by an intron of
CC   cyclin D1.  Human cyclin promoters D2 and D3 were isolated in the same
CC   manner.  Cyclin D1 has been shown to be expressed differentially in
CC   different cell types, with expression being highest in cells of neural
CC   origin.
SQ   Sequence   3158 BP;    952 A;    674 C;    722 G;    810 T;

  Query Match            6.8%;  Score 135;  DB 5;  Length 3158;
  Best Local Similarity  77.0%;  Pred. No. 1.64e-48;
  Matches   221;  Conservative    0;  Mismatches  62;  Indels   4;  Gaps   2;

Db  1653 ggccgggaacggtggctcacgcctgtaatcccagcacttttggaggccgagaccggcgga 1712
         || |||| |  |||||||||| ||| || |||||   |||| ||| |||||    || |||
Cp   293 GGACGGGTATAGTGGCTCACACCTATACTCCCAATGCTTTGGGAAGCCGAAGTGGGTGGA 234

Db  1713 tcac--gaggtcaggggttcaagactagcctggccaacatagtgaaaccccatctctacg 1770
         ||||  |||| |||| ||| |||| ||||||||||||||| |||||||||| | ||| |
Cp   233 TCACATGAGGCCAGGAGTTGGAGACCAGCCTGGCCAACATGGTGAAACCCCTTATCTGCT 174

Db  1771 aaaaatacaaaaattagtcaggcatggtggtgcgtgcctgtagtcccagctactcgggaa 1830
         ||||||||||||||||   ||||||||  | |  |||||| |||||||| | ||||||
Cp   173 AAAAATACAAAAATTAGCTGGGCATGGTAATACACACCTGTAATCCCAGCTATTTGGGAA 114

Db  1831 ttgcttgaacccgggaggtggaggttgcagtgagcccagatcgcaccactgcactccagc 1890
         |  |||||||| |||||||||||||||||||||| ||||||||||||||   ||||||
Cp   113 TCACTTGAACCCAGGAGGTGGAGGTTGCAGTGAGCCAAGATCGCACCACTGG--TCCAGC 56

Db  1891 ttgagcaacagagtagacttcgtctcaaaaaaaaaaaaaaaaaaaaa 1937
           || |||||||| |     ||  |||       ||||||| || |||
Cp    55 CTGGGCAACAGAGCAAGTCTCCCCTCTCCGCCCAAAAAAATAAGAAA 9


RESULT    3
ID   Q63862 standard; cDNA; 283 BP.
AC   Q63862;
DT   29-JAN-1995  (first entry)
DE   AP2 sequence obtd. by PCR for tumour specific DNA.
KW   Arbitrary primers; AP-PCR; amplification; tumour cells; cancer;
KW   insertions; deletions; ss.
OS   Synthetic.
PN   WO9411531-A.
PD   26-MAY-1994.
PF   12-NOV-1993; U10904.
PR   13-NOV-1992; US-975737.
PA   (CALB-) CALIFORNIA INST BIOLOGICAL RES.
PI   Ionov Y,  Malkhosyan S,  Mcclelland M,  Peinado MA;
PI   Perucho M,  Welshj;
DR   WPI; 94-183529/22.
PT   Identification of tumour cells - by analysing DNA to determine
PT   whether insertions or deletions have occurred in reiterated
PT   sequences
PS   Disclosure; Page 52; 67pp; English.
CC   The sequence was obtd. by PCR with arbitrary PCR primers used to
CC   detect insertions or deletions in DNA sequences.  Such mutations are
CC   markers of cancer so such primers can be used in the diagnosis of
CC   cancer, esp. colorectal, stomach or pancreatic tumours.
CC   See also Q63837-63.
SQ   Sequence   283 BP;    63 A;    77 C;    94 G;    49 T;

  Query Match            6.1%;  Score 121;  DB 11;  Length 283;
  Best Local Similarity  84.6%;  Pred. No. 8.37e-42;
  Matches   148;  Conservative    0;  Mismatches  27;  Indels   0;  Gaps   0;

Db     5 gggcgtggtggctcacacctgtaatcccagcactttgggaggccgaggtgggtggatcac 64
         |||  | |||||||||||||| || |||||   |||||||| ||||| ||||||||||||||
Cp   289 GGGTATAGTGGCTCACACCTATACTCCCAATGCTTTGGGAAGCCGAAGTGGGTGGATCAC 230

Db    65 ctgaggtcaggagttcaagaccagcctggccaacatggtgaaaccccgtctctactaaaa 124
         ||||| ||||||||  |||||||||||||||||||||||||||||||| | ||| ||||||
Cp   229 ATGAGGCCAGGAGTTGGAGACCAGCCTGGCCAACATGGTGAAACCCCTTATCTGCTAAAA 170

Db   125 atacaaaaattagccgggcgtggtggcgcgcgcctgtaatcccagctactcggga 179
         ||||||||||||||| |||| ||||    | | |||||||||||||||| | ||||
Cp   169 ATACAAAAATTAGCTGGGCATGGTAATACACACCTGTAATCCCAGCTATTTGGGA 115


RESULT    4
ID   Q94109 standard; DNA; 7849 BP.
AC   Q94109;
DT   22-FEB-1996  (first entry)
DE   hML genomic DNA.
KW   Human; thrombopoietin; TPO; mpl ligand; hML; fragment polypeptide;
KW   megakaryocytopoietic cytokine receptor; thrombopoietic signal;
KW   EPO-domain fragment; erythropoietin; hEPO; haematopoietic cell;
KW   megakaryocyte; thrombocytopenia; myeloproliferative disease;
KW   inflammatory thrombocytosis; iron deficiency; EPO; platelet;
KW   red blood cell; progenitor; hML-2; ss.
OS   Homo sapiens.
FH   Key             Location/Qualifiers
FT   prim_transcript 1166..7289
FT   /*tag= a
FT   exon            1161..1232
```